

Time course, cell types, and mechanism of induction of transforming growth factor betas following focal ischemia

Introduction: Transforming growth factor- β s (TGF- β 1-3) regulate the proliferation, differentiation, and survival of various cell types. TGF- β was suggested to be neuroprotective because injection of TGF- β decreased, while injection of an antagonist increased the infarct size following middle cerebral artery occlusion (MCAO) in rats.

Methods: The present study describes the induction of TGF- β 1-3 at 3h, 24h, 72h and 1 month after transient (1h) or permanent (24h) MCAO using in situ hybridization histochemistry and quantitative analysis. Double labeling with different markers was used to identify the localization of TGF- β mRNA relative to the penumbra and glial scar, and the types of cells expressing TGF- β s.

Results: TGF- β 1 expression increased 3h after MCAO in the penumbra. At 24h following MCAO, TGF- β 1 showed elevated expression level around the lesion. Most of TGF- β 1-expressing cells co-localized with IBA-1, a microglial marker, while a few TGF- β 1-expressing cells co-localized with GFAP, an astroglial marker. By 72h and 1 month after the occlusion, TGF- β 1 also appeared in microglia within the ischemic core and in the glial scar. In contrast, TGF- β 2 mRNA level was increased in neurons in layers II, III, and V of the ipsilateral cerebral cortex 24h after MCAO. None of the TGF- β 2-expressing cells contained GFAP or IBA-1 immunoreactivity. TGF- β 3 was not induced in cells around the penumbra. Its expression increased in only a few cells in layer II of the cerebral cortex 24h after MCAO. The levels of TGF- β 2 and - β 3 decreased at subsequent time points. Permanent MCAO further elevated the levels of all 3 subtypes of TGF- β s, it is likely that ischemia itself rather than reperfusion evokes the induction of TGF- β s. The area of TGF- β 1 expressing cells overlapped with Hsp70 a marker of the penumbra, but they were not present in the same cells. In contrast, TGF- β 2 expressing cells contained Hsp70 in the penumbra. TGF- β 1 did not co-localize with either Fos or ATF-3, while the co-localization of TGF- β 2 with Fos but not with ATF-3 suggests that cortical spreading depolarization, but not damage to neural processes, might be the mechanism of induction for TGF- β 2.

Conclusion: These data suggest that subtypes of TGF- β s are produced with different mechanisms in separate cell types after an ischemic attack, suggesting that they play a part in various neuroprotective and inflammatory processes.

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